REMARKS

Claims 1, 2, 5-16, 18-23 and 26-30 are pending in the present application. Claims 8, 9, 13-16, 20-22 and 27-29 have been withdrawn from further consideration as directed to a non-elected invention. Claims 1, 2, 5-7, 10-12, 18, 19, 23, 26 and 30 are therefore presently under consideration. The present examination is directed to a method of downregulating activin functional activity by introducing an activin antagonist wherein the antagonist is follistatin and wherein the specific condition is airway inflammation, an acute inflammatory response and targeting activin A.

Claim 6 has been amended as recommended by the Examiner thereby obviating the objection to Claim 6 of record.

Reconsideration of all the pending claims is respectfully requested in view of the following remarks.

The Examiner has rejected Claims 1, 2, 5-7, 10-12, 18, 19, 23 and 30 under 35 U.S.C. §102(b) as allegedly anticipated by U.S. Patent Publication 2003/0162715 (hereinafter "the '715 publication").

In the first instance, the phrase "activin antagonist" is very well understood by those skilled in the art, being a molecule which reduces the functionality or activity of a target. In the present case, the antagonistic molecules which are sought to be used are those which down regulate activin activity. This is consistent with the text which appears at page 34, lines 1-3 of the specification, for example, which discusses the use of molecules that decrease activin activity. Follistatin and the like are exemplified in this context at page 34.

The fact that a molecule can bind to a target, such as activin, does not make that molecule an antagonist in the sense that is required by the claims of the present invention, i.e.,

downregulating activin functional activity. FSTL-3, although able to bind to a limited subpopulation of activin molecules, does not function as an antagonist, as presently claimed. Due to its lack of a heparin binding site, which is a molecule that is expressed by follistatin, it cannot bind to cell surface proteoglycans. Heparin is part of the follistatin molecule and is not found in the FSTL-3 protein. In fact, at page 3595 of Sidis et al., *Endocrinology* 147:3586-3597, 2006 (hereinafter "Sidis, et al.), the authors specifically discuss this issue of differential activin regulating activity versus differential activin binding affinity. That is, the capacity of FSTL-3 to bind to activin is not necessarily related to its ability to regulate activin functionality, which is what is required by the claimed antagonists. Although FSTL-3 does have some ability to neutralize exogenous activin, it has extremely weak *in vivo* antagonistic activity, which is dependent on its interaction with endogenous activin. Accordingly, it does not interact satisfactorily with endogenous activin and is so weak in terms of its activity that it would not be regarded by any skilled person as functioning as an antagonist which is able to down-regulate activin related signaling at any useful level.

Sidis et al. very clearly state that the distinctions between FSTL-3 and follistatin support the understanding that the presence of a functional heparin binding site is a critical biochemical determinant for endogenous inhibition. Sidis, et al. acknowledge that FSTL-3 is regarded by those of skill in the art as unable to inhibit activin. Accordingly, whatever weak binding FSTL-3 may have with activin, it does not of itself render this molecule an antagonist as understood in the art and as required by the present claims, being that the antagonist decreases activin activity effectively (see page 34 of the specification). Sidis, et al. clearly state that in the absence of the heparin binding site, which FSTL-3 lacks, the molecule is unable to function to inhibit endogenous activin.

Still further, the '715 publication discloses and claims the FSTL-3 protein, *per se*. The disclosure of the '715 publication in relation to the potential uses for FSTL-3 are quite limited and certainly do not extend to the use of FSTL-3 to regulate activin and thereby inflammation. This is consistent with the fact that FSTL-3 is in fact not a functional antagonist of activin. In this regard, the Examiner cited paragraph 395 of the '715 publication. The Examiner contends that this paragraph discloses that FSTL-3 can be used for treating inflammatory conditions.

The claims of the present application are directed to downregulating the inflammatory response or treating a condition which is characterized by an unwanted inflammatory response. At page 20 of the present specification, the reference to "inflammatory response" in the claims is defined to include the physiological and immunological events which occur in the context of inflammation. These are essentially summarized in points (i)-(v) in the middle of page 20 of the specification. The specification reflects that prior to reaching the point that the cells of the immune system proliferate, there is significant physiological activity which is the result of the complex cytokine cascade which unfolds early in the inflammatory process. At page 8 of the specification it clearly indicates that the findings in relation to this invention relate to the fact that activins A and B are found to be crucial components in this cytokine cascade which underpins the inflammatory response.

Page 395 of the cited reference, however, discusses the role of FSTL-3 in the context of modulating inflammation at the level of inhibiting the proliferation and differentiation of cells involved in inflammation. Accordingly, it is clear from the reference that FSTL-3, at best, can only act separately from the cytokine cascade, which forms an integral component of the inflammatory response, i.e, to down regulate the proliferation and

differentiation of cells which are involved in an inflammatory condition.

Notably, the inflammatory response precedes the process of immune cell differentiation and proliferation. These are distinct processes and temporarily separated. Targeting the inflammatory response at the cellular level, which is all that the '715 publication teaches, does not lend any teaching to targeting the cytokine cascade. Since FSTL-3 cannot act as an effective activin antagonist, it cannot be concluded that the use of FSTL-3 would achieve the outcome presently claimed, i.e., downregulating an inflammatory response.

Moreover, the '715 publication further states that FSTL-3 or antagonists of FSTL-3 may inhibit the proliferation and differentiation of cells. Either FSTL-3 inhibits proliferation and differentiation or it does not. However, that this molecule and its antagonist could both achieve the same cellular outcome is not physiologically possible and is indicative of the fact that the teaching at page 395 is contradictory, even nonsensical and therefore is not an appropriate reference relative to the present claims. This contradiction is actually consistent with the fact that FSTL-3 is not a functional antagonist of activin and, therefore, even if the role of activin had been known in terms of inflammation, FSTL-3 could not have been used to down-regulate the cytokine cascade which underpins inflammation.

Still further, it is certainly the case that in the context of the present invention, the use of an antagonist to follistatin would, in fact, lead to up regulation of the inflammatory response since follistatin would be unable to bind to and inhibit the functionality of activin. Accordingly, if the teachings at page 395 of the '715 publication are followed literally, the inflammatory response may well be up regulated. The teachings of the '715 publication clearly fail to anticipate the subject matter of the present claims.

The Examiner has also rejected Claims 1, 2, 5-7, 10-12, 18, 19, 23, 26a and 30

under 35 U.S.C. §102(b) as allegedly anticipated by WO 03/006006057 (hereinafter "the '057 publication).

In response to the Examiner's rejection, Applicants observe that fibrosis occurs subsequently to an inflammatory response but is not an inflammatory response itself, it is a form of scarring. The fact that inflammation and fibrosis may occur sequentially is irrelevant. Even if fibrosis is successfully treated, i.e., the scarring is prevented, this does not necessarily mean that such result has been achieved via down-regulation of an inflammatory response which may have preceded it. Fibrosis and the processes that lead to scarring are extremely complex and one can treat fibrosis at the level of the cellular events which occur in the context of the fibrotic process itself.

The Examiner asserts that the '057 publication teaches the use of follistatin in the treatment of diseases associated with fibrosis such as interstitial lung disease, which is airway inflammation. There is no dispute that fibrosis can occur after an inflammatory response. This is the case with interstitial lung disease, where an inflammatory response ultimately leads to development of fibrotic tissue. However, follistatin in this context is still taught to be used in the context of modulating the fibrotic processes, not the inflammatory processes. Although the diseases which are listed at page 3, lines 30-33 of the cited reference mention inflammatory fibrotic diseases, the fact is that this disclosure is still directed to treating the fibrotic processes, not the inflammatory aspect of this disease. There is no teaching in the '057 publication of the modulation of the inflammatory response, such as an inflammatory response which does not lead to a fibrotic outcome. This is because the applied reference is directed to the cellular events of fibrosis, which occur separately and subsequently to an earlier inflammatory response.

For example, the effects of the inflammatory cytokine cascade are critical to the

managment of septicemia which kills patients well before the fibrotic response commences. Notably, in the cited reference (see examples) mice die within twenty-four hours of an LPS challenge, i.e., well before a fibrotic response can occur. Follistatin can prevent this mortality.

The cited art teaches that in any condition where fibrosis occurs, irrespective of whether it is preceded by an inflammatory response, follistatin can be used to down regulate the fibrotic events. This is entirely different to that which is claimed in the present application wherein one can modulate an inflammatory response, irrespective of whether or not fibrosis occurs. At best, the '057 publication teaches that where a fibrotic outcome is associated with an inflammatory condition, at least the tissue scarring aspect can be down-regulated, but the patient endures the preceding inflammatory response. It is simply that the scarring side effect associated with tissue damage can be down regulated by follistatin, but not that the preceding inflammatory response which is endured by the patient could be in any way relieved.

Fibrosis is an extremely complex cellular event. There are many molecules which will stimulate fibroblasts to divide. The fact that the '057 publication teaches that follistatin can down regulate fibroblast stimulation does not teach anything about the regulation of inflammatory responses. Still further, since many inflammatory responses are not associated with fibrosis, and fibrosis occurs at a later timepoint to inflammation, the cited reference is completely distinguished. Accordingly, the '057 publication does not anticipate the claimed invention.

Claims 1, 2, 5-6, 10-11, 18, 19, 23, 26 and 30 have also been rejected under 35 U.S.C. §102(b) as allegedly anticipated by WO 8911862 (hereinafter "the '862 publication").

The Examiner alleges that the '862 publication teaches that inhibin is useful in

wound healing, autoimmune disease, immunodeficiency disease, transplant rejection and infection. Applicants respectfully submit that the cited reference actually teaches away from the present invention.

In the first instance, the cited reference is directed to the identification of the role of inhibin in the context of modulating the immune response. The Examiner states that we are "reminded that no more of the reference is required than that it sets forth the substance of the invention and that any claimed functional limitations would be inherent properties of the inhibin polypeptide in the absence of evidence to the contrary". However, the prior art reference is directed to the role of inhibin in the context of regulating the immune response. Immune responses are extremely complex. Such responses include an inflammatory component which is central to the initial nonspecific/innate immune response. Subsequent to prolonged challenge with an antigen, there will be initiated a specific immune response which is characterized by the activation and proliferation of T cells and B cells. It is generally understood that the non-specific immune response will assist in achieving a good specific immune response.

The '862 reference, however, focuses on the role of inhibin in the context of T cell and B cell activity, i.e., the specific immune response. The reference states that inhibin stimulates the proliferation of lymphocytes. Immunization of rabbits with inhibin, which produces antibodies to inhibin, was shown to result in suppression of immunoglobulin levels.

Accordingly, these findings teach that inhibin is a stimulator of the immune response. Based on these findings, the cited reference teaches that inhibin is useful in the context of wound healing, autoimmune diseases, immunodeficiency, transplant rejection and infection, as specified by the Examiner.

However, the '862 reference actually teaches away from the present invention. The reference teaches that inhibin is immunostimulatory. Accordingly, inhibin stimulates the immune system. At any level, one skilled in the art would associate immune stimulation with up regulation of an inflammatory response since this is part of the immune response. This is, in fact, the basis upon which immunization works where adjuvants are administered in order to stimulate an inflammatory response and to thereby assist in developing good specific immunity.

The cited reference actually does not provide any specific disclosure in relation to inflammation. However, if one is attempting to stimulate the immune response, one would not be down regulating the inflammatory response. At best, the '862 publication does not teach anything in the context of inflammation.

In terms of treating wounds, the applied reference teaches the administration of activin, not inhibin. No disclosure is provided in relation to the role of inhibin in the context of wound healing. Even in the context of infection, the '862 publication teaches that inhibin is used to stimulate the immune response.

Infections are routinely associated with inflammation, as indicated by the Examiner at page 5 of the Office Action; infection is associated with an inflammatory response to bacterial infection. At page 5, line 5 of the '862 publication, it is clearly stated that inhibin is administered in this situation to "stimulate the immune system response to infections". Accordingly, the reference is teaching the opposite of the claimed subject matter. The Examiner, however, has asserted that the reference to treating infection is in the context of down regulating the inflammatory response. In fact, the opposite is taught by this prior art reference. Any method which teaches up regulating the immune response cannot be interpreted to indicate that the inflammatory response is down-regulated since inflammation is a normal part of the

early immune response.

The claims of the present invention are directed to down regulating the inflammatory response even in the context of infection. It is now known that the inflammatory response, albeit a normal part of an immune response, can itself be dangerous. However, one must be cautious with down regulating the inflammatory response, which is a normal part of an immune response, to ensure that clearance of the pathogen is nevertheless effected, such as via the administration of antibiotics or the like. For example, with influenza it is often the inflammatory response which actually kills patients suffering from influenza, and not the virus itself. It is for this reason that the ability to down regulate the inflammatory aspect of the immune response, which is the normal early stage of the immune response to infection, can be so valuable in such patients since it is not the virus which kills these patients, but the rapid and uncontrolled inflammatory response which, if down regulated, does give the patient an opportunity to survive. The cited prior art simply teaches that inhibin can stimulate the immune response to infection in order to clear the infection. The reference draws no distinction between different aspects of the immune response.

Accordingly, the prior art reference actually teaches away from the claimed subject matter of the present application. The regulation of the specific immune response simply does not teach anything about the regulation of the inflammatory response, which occurs early in the immune response pathway.

The present application claims down regulating an inflammatory response or treating a condition characterized by an inflammatory response by down regulating that inflammatory response. There is nothing disclosed in the '862 publication in relation to inflammatory responses nor is there even disclosure which would arguably inherently

demonstrate that this outcome was achieved since the reference claims that inhibin is an immunostimulator. This teaching indicates that inhibin up regulates all aspects of the immune system, including inflammation since this is a recognized outcome of immune stimulation. Accordingly, the '862 publication fails to anticipate the claimed invention.

The Examiner has rejected Claims 1, 2, 507, 10-12, 18, 19, 23, 26 and 30 under 35 U.S.C. §102(b) as allegedly anticipated by U.S. Patent Publication 2002/0192216 (hereinafter 'the '216 publication). The '216 publication teaches that follistatin is an inhibitor of the Hedgehog signaling pathway. This pathway does not include activin and it is therefore not entirely clear how this prior art reference is relevant to the claimed invention. Inflammation is an extremely complex process which involves multiple signaling pathways. Hedgehog plays a role in this context but is a different and distinct pathway to that which has been identified in the context of the present invention. The fact that the present inventors have determined that activin is a crucial molecule in terms of the inflammatory cytokine cascade has provided an alternative means of treating inflammatory conditions based on antagonizing activin.

Applicants observe that the reference identifies BMPs as blocked by follistatin. The affinity of follistatin for BMPs however is less than 10% of the affinity for activin A. Further, the action of follistatin to block BMP has not used an inflammatory end point. Notably, many factors using different pathways stimulate inflammation and the ultimate result of these actions can only be tested *in vivo*.

Further, Hedgehog is an intracellular signaling molecule. Activin is not an intracellular signaling molecule. The '216 publication is based **on** binding a molecule to the cell surface which sends a signal internally to down regulate Hedgehog signaling intracellularly or, presumably, to use a molecule which can be internalized by a cell in order to down regulate

Hedgehog signaling. Activin is not an intracellular signaling molecule and one skilled in the art would not assume that any molecule which can down regulate intracellular signaling would necessarily have any role in terms of down regulating extracellular cytokine functionality as a means to down regulate the cytokine cascade which underpins the inflammatory response. This cytokine cascade is not an intracellular mechanism. In fact, a molecule which is shown to impact intracellular signaling is self evidently one that binds to or is internalized by a cell. This understanding does not lead one to conclude that such a molecule would act as an antagonist of an extracellular cytokine, especially one that plays no evident role in that signaling pathway.

The '216 publication is irrelevant to modulating extracellular cytokine cascades and the functionality of those cytokines in the context of down regulating inflammation. Activin is not an intracellular molecule involved in the Hedgehog pathway, it is a cytokine which is produced and secreted by cells as a result of an intracellular signal. However, the cited reference merely discloses that the Hedgehog signaling pathway leads to secretion of the BMP protein. The reference does not suggest that activin production is the result of Hedgehog signaling or that Hedgehog signaling would otherwise play any role in activin production or functionality. Although BMP and activin are both members of the TNFβ superfamily, this of itself does not suggest that all of the molecules of the TNFβ superfamily are produced by the same intracellular signaling mechanism.

Cytokines, such as follistatin, are pleiotropic. Accordingly, the fact that follistatin may be shown to down regulate Hedgehog which therefore down regulates Hedgehog signaling and prevents production of BMP, does not inherently teach that which is claimed in the present application, i.e., that activin is in fact the crucial cytokine which regulates the inflammatory response and that antagonizing activin will achieve an effective anti-inflammatory

response. The cited reference teaches that follistatin is an inhibitor of an intracellular signaling pathway, but provides absolutely no disclosure or teaching of the role of follistatin in the context of regulating the extracellular cytokine cascade via its regulation of extracellular protein molecules, such as activin. Accordingly, the '216 publication does not anticipate the subject matter of the claimed invention.

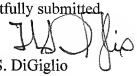
The Examiner has rejected Claims 1, 2, 5-7, 10-12, 18, 19, 23, 26 and 30 under 35 U.S.C. §112, first paragraph, as failing to evidence possession of the claimed invention at the time of filing the application. Specifically, the Examiner alleges that there is no written description for "an activin antagonist" wherein the antagonist is a "proteinaceous molecule".

In this regard, the Examiner's attention is respectfully directed to the disclosure of the specification, particularly at page 31, *et seq.* commencing at line 9 (see, also particularly pp. 32 and 34). Specifically, "an activin antagonist" is well understood by one skilled in the art as a molecule which reduces the functionality or activity of a target. Various means are readily available to the skilled artisan to determine whether a candidate molecule is an activin antagonist. These features as well as an articulation of what is meant by proteinaceous and non-proteinaceous antagonists are provided at the cited disclosures. The skilled artisan would readily recognize that the inventors were in possession of the claimed invention at the relevant time.

Accordingly, the rejection under 35 U.S.C. §112, first paragraph, is obviated and withdrawal thereof is respectfully requested.

In view of the foregoing amendments and remarks, it is firmly believed that the subject application is in condition for allowance, which action is earnestly solicited.

Respectfully submitted,



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